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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SANG, HONG	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,359	YANG ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *1-28 and 40-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/18/03 and 9/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibits A*.

DETAILED ACTION

RE: Yang et al.

1. Applicant's election of Group II (claims 29-39) and SEQ ID NOS 4 and 16 in the reply filed on 12/19/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicants are reminded that election of SEQ ID NO.4 and SEQ ID NO.16 is a restriction requirement not election of species (see previous office mailed on 6/1/2006, page 3, lines 1-3).

3. The information disclosure statements (IDS) filed on 11/18/03 and 9/23/04 have been considered. Signed copies are attached hereto.

4. Claims 1-62 are pending. Claims 1-28 and 40-62 are withdrawn from further consideration as being drawn to non-elected inventions.

5. Claims 29-39 are under examination.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code see page 12, line 12, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code found throughout the specification. See MPEP § 608.01.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 29-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to an isolated polypeptide wherein said polypeptide comprises (a) an amino acid sequence set forth in SEQ ID NO. 16; (b) an amino acid sequence having at least about 90%, 95%, or 98% identity with an amino acid sequence set forth in SEQ ID NO.16; (c) an amino acid sequence encoded by a nucleic acid that hybridizes under stringent conditions to the complementary strand of a nucleic acid having a sequence set forth in SEQ ID NO. 4; or (d) a fragment of an amino acid sequence set forth in SEQ ID NO.16 (see claims 29, 35 and 36). The claims are further limited wherein said polypeptide has one or more of the following biological activities: (i) binds a target DNA sequence, (ii) transactivates a target gene, (iii) induces apoptosis, (iv) oligomerizes, (v) localizes to basal epithelial cells, or (vi) localizes to squamous cervical cells. The phrase "said polypeptide comprises **an** amino acid sequence set forth in SEQ ID NO.16" recited in claims 29 and 37, for example reads on comprising fragments of SEQ ID NO.16, which can be as small as two amino acid residues. Therefore,

applicants are claiming a genus of polypeptides that encompass a homolog, a variant, and a fragment of SEQ ID NO.16 with or without the biological properties representative of SEQ ID NO.16 (see claim 29, for example). While claims 30 and 31 limit the polypeptides to those who have certain functions (e.g. binding to a target sequence), the specification fails to provide sufficient descriptive information such as a core structure that is required for the function (e.g. binding to a target sequence or transactivates a target gene), and is common to the genus of the sequences that are at least 90%, 95%, or 98% identical to an amino acid sequence set forth in SEQ ID NO.16, and a fragment of SEQ ID NO.16. Moreover, the terms "target sequence" and "target gene" recited in claim 30 do not reference to a specific sequence or gene. The specification only teaches a p53 target binding sequence. Applicants are claiming a genus of homologs and fragments with or without the biological properties representative of SEQ ID NO.16. However, the written description in this case only sets forth an isolated polypeptide consisting of SEQ ID NO. 16, therefore the written description is not commensurate in scope with the claims which read on any homologs that are at least 90%, 95% or 98% identical to SEQ ID NO.16 and any and all fragments of SEQ ID NO. 16. There is a lack of a written description regarding which amino acids within the full-length amino acid sequence of SEQ ID NO. 16 that can be changed by deletion, addition, substitution and combination thereof such that the resulting variant, or homolog that have alterations in amino acid sequence of SEQ ID NO.16 still have the same function as the polypeptide of SEQ ID NO. 16, such as binding to a target sequence or transactivates a target gene. There is a lack of a written description

regarding which fragments of SEQ ID NO. 16 would have the same function as the polypeptide of SEQ ID NO. 16. Moreover, there is a lack of a written description regarding the amino acid sequence encoded by a nucleic acid that hybridizes under stringent conditions to the complementary strand of a nucleic acid of SEQ ID NO.16. The nucleic acid that hybridizes under stringent condition encompasses the nucleic acids that hybridize only to the partial sequence of SEQ ID NO.16. The polypeptide that is encoded by the nucleic acid that hybridizes to a partial sequence of SEQ ID NO.16 would not be expected to have same function as SEQ ID NO.16. Moreover, the claims do not limit the hybridization condition to highly stringent, therefore, the nucleic acids that hybridizes under low stringent condition to SEQ ID NO.16 would not be expected to encode the polypeptide that has same function as SEQ ID NO. 16. There is a lack of a written description regarding the structure and the function of the polypeptide encoded by such nucleic acids: Furthermore, there is a lack of written description regarding the target sequence and target gene that are recited in claim 30. Applicant does not appear to have reduced to practice any variant, homolog or fragment that have alterations in amino acid sequence of SEQ ID NO. 16. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Although drawn to DNA arts, the findings in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University Of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The Court stated that" [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> *a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the*

gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. V. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics .... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in *Lilly* and *Enzo* were DNA constructs *per se*, the holdings of those cases are also applicable to claims such as those at issue here. Thus the instant specification may provide an adequate written description of a

polypeptide that is at least 90%, 95%, or 98% identical to SEQ ID NO. 16 or a fragment of SEQ ID NO.16 by structurally describing representative homologs or fragment by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe a polypeptide that is at least 90%, 95%, or 98% identical to SEQ ID NO. 16 or a fragment of SEQ ID NO.16 useful in the claimed invention in a manner that satisfies either the *Lilly* or *Enzo* standards. Although the specification discloses SEQ ID NO.16, it is broadly described and this does not provide a description of the broadly claimed homologs and fragments of SEQ ID NO.16 that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe a polypeptide that is at least 90%, 95%, or 98% identical to SEQ ID NO. 16 or a fragment of SEQ ID NO.16 by the test set out in *Lilly* because the specification describes only SEQ ID NO. 6 (i.e. full length). Therefore it necessarily fails to describe a representative number of such species. Thus the specification does not provide an adequate written description of a polypeptide that is at least 90%, 95%, or 98% identical to SEQ ID NO. 16 or a fragment of SEQ ID NO.16 that is required to practice the claimed invention.

Therefore, the specification provides neither a representative number of the homologs and fragments, nor does it provide a descriptive of structural features that are common to the homologs and fragments. The instant specification fails to provide sufficient descriptive information such as a core structure that is required for the function (e.g. binding to a target sequence) and is common to the genus of the sequences that are at least 90%, 95% or 98% identical to SEQ ID NO.16 and fragments thereof. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a single species is insufficient to describe a highly variant genus. Because the genus of molecules encompassed by genus of the homologs and fragments is extensive and the artisan cannot envision the detailed structure of the encompassed variants, homologs and fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus one of skill in the art would not be able to recognize that applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the

subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Therefore, only SEQ ID NO.16 but not the full breadth of the variants, homologs or fragments of SEQ ID NO. 16 meet the written description provision of 35 U.S.C. § 112 first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

9. Claims 29-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide of SEQ ID NO. 16, does not reasonably provide enablement for an isolated polypeptide that is at least 90%, 95%, 98% to SEQ ID NO.16, a fragment of SEQ ID NO.16, and an amino acid sequence encoded by a nucleic acid that hybridizes under stringent conditions to the complementary strand of a nucleic acid having a sequence set forth in SEQ ID NO. 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 37 is included in this rejection because the phrase "said polypeptide comprises **an** amino acid sequence set forth in SEQ ID NO.16" reads on any fragments as small as two amino acids of SEQ ID NO.16. The rejection to claim 37 can be obviated by amending the claim to change the word "**an**" to the word "the".

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims are drawn to an isolated polypeptide wherein said polypeptide comprises (a) amino acid sequence set forth in SEQ ID NO. 16; (b) an amino acid sequence having at least about 90%, 95%, or 98% identity with an amino acid sequence set forth in SEQ ID NO.16; (c) an amino acid sequence encoded by a nucleic acid that hybridizes under stringent conditions to the complementary strand of a nucleic acid having a sequence set forth in SEQ ID NO. 4; or (d) a fragment of an amino acid sequence set forth in SEQ ID NO.16 (see claims 29, 35 and 36). The claims are further limited wherein said polypeptide has one or more of the following biological activities: (i) binds a target DNA sequence, (ii) transactivates a target gene, (iii) induces apoptosis, (iv) oligomerizes, (v) localizes to basal epithelial cells, or (vi) localizes to squamous cervical cells.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Applicants broadly claim a genus of an isolated polypeptide that comprises homologs, fragments and variants of SEQ ID NO.16, and the amino acid sequence encoded by a nucleic acid that hybridizes under stringent conditions to the complementary strand of a nucleic acid of SEQ ID NO.4.

The "target sequence" recited in claim 30 reads on any sequences to which the homologs, fragments and variants of SEQ ID NO.16 can bind. The "target gene" recited in claim 30 reads on any gene that could be regulated or affected by the homologs, variants, and fragments of SEQ ID NO.16.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the structure and effects of a polypeptides that are at least 90%, 95% or 98% identical to SEQ ID NO. 16, or a fragment of SEQ ID NO.16. Moreover, it would require significant study to determine which of the amino acids that are at least 90%, 95% or 98% identical to SEQ ID NO. 16, or a fragment of SEQ ID NO.16 in fact have the same function as SEQ ID NO.16. The identification and characterization of each of these protein homologs and fragments would be inventive, unpredictable, and

difficult in itself, requiring years of inventive effort with no guarantee of success in doing so.

Moreover, because the claim does not define that the hybridization conditions are highly stringent and because non-specific binding occurs at low stringent conditions, one of skill in the art would expect substantial variation among species encompassed within the scope of the claim. The nucleic acids that bind non-specifically to SEQ ID NO. 2 would encode the proteins that have different functions from SEQ ID NO.16. Therefore, one of skill in the art would not know how to use these proteins encoded by the nucleic acids that hybridize under stringent conditions to SEQ ID NO.4. Furthermore, a nucleic acid that hybridizes under stringent condition to SEQ ID NO.4 encompasses those that hybridize to the partial sequence of SEQ ID NO.4. The specification does not teach how to use the polypeptides that are encoded by such nucleic acids.

The state of the prior art and the predictability or lack thereof in the art:

Schmale et al. (Oncogene, 1997, September, 15: 1363-1367, IDS) teach a rat KET polypeptide with strong homology to the tumor suppressor p53 (see abstract). The sequence of the rat KET polypeptide of Schmale et al. is 98.3% identical (best local similarity) to the instant SEQ ID NO.16 (see sequence alignment, Exhibit A). Schmale et al. teach that the KET polypeptide may play a role in cell-cycle control or apoptosis (see page 1365, 3rd paragraph). Aside from the KET polypeptide, the prior art does not

teach any other homologs or fragments of SEQ ID NO.16 that have the same function as SEQ ID NO.16.

One cannot extrapolate the teachings of the specification and the prior art to the scope of the claims because the claims are broadly drawn to any isolated polypeptides that are at least 90%, 95% or 98% identical to SEQ ID NO. 16, or a fragment of SEQ ID NO.16 with or without the biological properties representative of SEQ ID NO.16, and applicant has not enabled all of the polypeptides because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the

biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all homologs, variants and fragments with sequence similarity to the amino acid sequence of SEQ ID NO.16. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Working examples:

The specification teaches a method for cloning p63 cDNAs (See working example VI, page 106). Based on the teaching of the specification, one of ordinary skilled in the art would know how to make the p63 polypeptide of SEQ ID NO.16 and the polypeptide encoded by the nucleic acid consisting of SEQ ID NO.4. However, the specification fails to teach any other embodiments of the genus, i.e. homologs and fragments of SEQ ID NO.16 that have the same biological function of SEQ ID NO.16. One would not know if a polypeptide with the claimed homology would function as the protein of SEQ ID NO. 16. The specification has not taught any polypeptide that is at least 90%, 95% or 98% homologous to SEQ ID NO. 1 would function as SEQ ID NO.16. Therefore, one skilled in the art cannot envision the detailed structures of the genus. Without such information, one skill in the art cannot practice the claimed invention.

Guidance in the specification

While one of ordinary skill in the art can theoretically produce all of these polypeptides with art known techniques such as site-directed mutagenesis it would still be burdensome to one of ordinary skill in the art to produce all of these different combinations and thereafter determine their function. It is art known that certain residues are shown to particularly important to the biological or structural properties of a protein or peptide, e.g., residues in active sites and such residues may not be generally be exchanged. Skolnick et al teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (Skolnick, et al. Trends in Biotech. 18, 34-39, 2000, see abstract, in particular). Given

the unlimited number of undisclosed polypeptides, there is no working example demonstrating the undisclosed polypeptides can function as SEQ ID NO. 1. Moreover, it is not clear what criteria would be used in deciding which amino acids and how many of them would and could be substituted in SEQ ID NO. 16. Without such guidance, the changes which can be made in SEQ ID NO. 16 and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Further, stringent conditions encompass from low, medium to high stringency (see specification page 31, lines 28-29). As conventionally understood in the art and as taught by US Patent No. 5;912,143, hybridization is used to refer to any process by which a strand of nucleic acid binds with a complementary strand through base pairing (col 5, lines 3-5) and further teaches that numerous equivalent conditions may be employed to comprise either low or high stringency conditions and hybridization solutions my be varied to generate conditions of either low or high stringency (col 5, lines 57-67). The "stringent hybridizing" as claimed read on both high and low stringency conditions. It is well known that the lower the stringency condition the more dissimilar the hybridizing molecule will be from the molecule to which it hybridizes. For example, Sambrook et al, eds, 1989, 2nd ed, Molecular Cloning, a laboratory manual,

Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 11.52, teach that the temperature of hybridization, (which is related to the degree of stringency) should be high enough to suppress hybridization of the probe to incorrect sequences. Sambrook et al further teach that if the probe hybridizes indiscriminately, repeat the hybridization at a higher temperature or wash under conditions of higher stringency (p. 11.52, last two lines). Because an unrelated polynucleotide could hybridize with the polynucleotide of SEQ ID NO:4, via a common fragment, even under the most stringent hybridization conditions, the polypeptide encoded by such unrelated polynucleotide would not expected to have the same structure or function as the polypeptide encoded by SEQ ID NO.4. Furthermore, because the nucleic acid that hybridizes under high stringency conditions to SEQ ID NO.4 encompasses nucleic acid fragments as small as four nucleotides (as long as they can hybridize under stringency condition to SEQ ID NO.4), the polypeptide encoded by such nucleic acid fragment would not function like the protein encoded by SEQ ID NO.16. Therefore, one of skill in the art would not know how to use the full scope of the polypeptide of the claim 29 part (c). In view of the above, one of skill in the art would be forced into undue experimentation in order to use the claimed invention as broadly as claimed.

Level of skill in the art

The level of the skill in the art is deemed to be high

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 29-31, and 34-39 are rejected under 35 U.S.C. 102(a) as being anticipated by Schmale et al. (Oncogene, 1997, September, 15: 1363-1367, IDS).

Schmale et al. teach a KET polypeptide with strong homology to the tumor suppressor p53 (see abstract). The sequence of the mammalian KET polypeptide of Schmale et al. is 98.3% identical (best local similarity) to the instant SEQ ID NO.16 (see sequence alignment, Exhibit A). Schmale et al. teach that the human KET polypeptide has been sequenced but has not been published (see page 1363, right column, 2nd paragraph, line 12). Schmale et al. teach that the KET polypeptide is localized in skin epidermis, and may play a role in cell-cycle control or apoptosis (see page 1365, 3rd

paragraph). Moreover, because the polypeptide of Schmale et al. shares strong homology to p53 (see abstract) and is 98.3% identical to the instant SEQ ID NO.16, it would be capable of binding to a p53 responsive element.

Moreover, claims 29 and 39 recite "comprising **an** amino acid sequence set forth in SEQ ID NO.16", claims read on fragments of SEQ ID NO.16, which are as small as two amino acid residues. Because human p53 comprises at least two amino acid residue of SEQ ID NO. 16 (see Fig.1), therefore, Schmale et al. teaches limitation of claims 29 part (a) and 39.

Conclusion

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Jan. 3, 2007

CHRISTOPHER H. YAEN
PRIMARY EXAMINER

Exhibit A

```
<!--StartFragment-->RESULT 5
P73L_RAT
ID   P73L_RAT       STANDARD;      PRT;   680 AA.
AC   Q9JJP6; Q99JD6; Q99JD7; Q99JD8; Q99JD9; Q99JE0; Q99JE1; Q99JE2;
AC   Q99JE3;
DT   04-JAN-2005, integrated into UniProtKB/Swiss-Prot.
DT   01-OCT-2000, sequence version 1.
DT   07-FEB-2006, entry version 29.
DE   Tumor protein p73-like (p73L) (p63) (Transformation-related protein
DE   63) (TP63) (Keratinocyte transcription factor KET).
GN   Name=Tp73l; Synonyms=Ket, P63, Trp63;
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi;
OC   Muroidea; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 1), AND TISSUE SPECIFICITY.
RC   TISSUE=Lingual epithelium;
RX   MEDLINE=97460723; PubMed=9315105; DOI=10.1038/sj.onc.1201500;
RA   Schmale H., Bamberger C.;
RT   "A novel protein with strong homology to the tumor suppressor p53.";
RL   Oncogene 15:1363-1367(1997).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [MRNA] (ISOFORMS 2; 3; 4; 5; 6; 7; 8 AND 9),
RP   FUNCTION, AND TISSUE SPECIFICITY.
RC   STRAIN=Wistar; TISSUE=Tongue;
RX   MEDLINE=21363378; PubMed=11470269; DOI=10.1016/S0014-5793(01)02643-6;
RA   Bamberger C., Schmale H.;
RT   "Identification and tissue distribution of novel KET/p63 splice
RT   variants.";
RL   FEBS Lett. 501:121-126(2001).
CC   -!- FUNCTION: Acts as a sequence specific DNA binding transcriptional
CC       activator or repressor. The isoforms contain a varying set of
CC       transactivation and auto-regulating transactivation inhibiting
CC       domains thus showing an isoform specific activity. May be required
CC       in conjunction with TP73/p73 for initiation of TP53/p53 dependent
CC       apoptosis in response to genotoxic insults and the presence of
CC       activated oncogenes. Involved in Notch signaling by probably
CC       inducing JAG1 and JAG2. Plays a role in the regulation of
CC       epithelial morphogenesis. The ratio of DeltaN-type and TA*-type
CC       isoforms may govern the maintenance of epithelial stem cell
CC       compartments and regulate the initiation of epithelial
CC       stratification from the undifferentiated embryonal ectoderm.
CC       Required for limb formation from the apical ectodermal ridge (By
CC       similarity).
CC   -!- COFACTOR: Binds 1 zinc ion per subunit (By similarity).
CC   -!- SUBUNIT: Binds DNA as a homotetramer. Isoform composition of the
CC       tetramer may determine transactivation activity. Interacts with
CC       HIPK2 (By similarity).
CC   -!- SUBCELLULAR LOCATION: Nucleus (By similarity).
CC   -!- ALTERNATIVE PRODUCTS:
CC       Event=Alternative promoter;
CC         Comment=3 isoforms, 1 (shown here), 7 and 2, are produced by use
CC         of alternative promoters;
CC       Event=Alternative splicing; Named isoforms=9;
CC       Name=1; Synonyms=TA2-alpha;
CC         IsoId=Q9JJP6-1; Sequence=Displayed;
CC       Name=2; Synonyms=DeltaN-alpha;
CC         IsoId=Q9JJP6-2; Sequence=VSP_012475;
CC       Name=3; Synonyms=TA2-beta;
CC         IsoId=Q9JJP6-3; Sequence=VSP_012478;
CC         Note=Produced by alternative splicing of isoform 1;
CC       Name=4; Synonyms=DeltaN-beta;
CC         IsoId=Q9JJP6-4; Sequence=VSP_012475, VSP_012478;
```

Exhibit A

```
CC         Note=Produced by alternative splicing of isoform 2;
CC       Name=5; Synonyms=TA2-gamma;
CC         IsoId=Q9JJP6-5; Sequence=VSP_012477;
CC         Note=Produced by alternative splicing of isoform 1;
CC       Name=6; Synonyms=DeltaN-gamma;
CC         IsoId=Q9JJP6-6; Sequence=VSP_012475, VSP_012477;
CC         Note=Produced by alternative splicing of isoform 2;
CC       Name=7; Synonyms=TA1-alpha;
CC         IsoId=Q9JJP6-7; Sequence=VSP_012476;
CC       Name=8; Synonyms=TA1-beta;
CC         IsoId=Q9JJP6-8; Sequence=VSP_012476, VSP_012478;
CC         Note=Produced by alternative splicing of isoform 7;
CC       Name=9; Synonyms=TA1-gamma;
CC         IsoId=Q9JJP6-9; Sequence=VSP_012476, VSP_012477;
CC         Note=Produced by alternative splicing of isoform 7;
CC   -!- TISSUE SPECIFICITY: Widely expressed, notably in thymus, prostate,
CC       placenta, and skeletal muscle, although the precise isoform varies
CC       according to tissue type. Progenitor cell layers of skin, breast
CC       and prostate express high levels of DeltaN-type isoforms.
CC   -!- DOMAIN: The transactivation inhibitory domain (TID) can interact
CC       with, and inhibit the activity of the N-terminal transcriptional
CC       activation domain of TA*-type isoforms (By similarity).
CC   -!- PTM: May be sumoylated (By similarity).
CC   -!- SIMILARITY: Belongs to the p53 family.
CC   -!- SIMILARITY: Contains 1 SAM (sterile alpha motif) domain.
CC   ----------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ----------------------------------------------------------------------
DR   EMBL; Y10258; CAB88216.1; -; mRNA.
DR   EMBL; AJ277446; CAC37098.1; -; mRNA.
DR   EMBL; AJ277447; CAC37099.1; -; mRNA.
DR   EMBL; AJ277448; CAC37100.1; -; mRNA.
DR   EMBL; AJ277449; CAC37101.1; -; mRNA.
DR   EMBL; AJ277450; CAC37102.1; -; mRNA.
DR   EMBL; AJ277451; CAC37103.1; -; mRNA.
DR   EMBL; AJ277452; CAC37104.1; -; mRNA.
DR   EMBL; AJ277453; CAC37105.1; -; mRNA.
DR   HSSP; Q9NP68; 1GZH.
DR   SMR; Q9JJP6; 544-610.
DR   Ensembl; ENSRNOG00000001924; Rattus norvegicus.
DR   RGD; 620863; Trp63.
DR   InterPro; IPR002117; P53.
DR   InterPro; IPR011615; P53_DNA_bd.
DR   InterPro; IPR012346; P53_RUNT_DNA_bd.
DR   InterPro; IPR010991; p53_tetrameristn.
DR   InterPro; IPR001660; SAM.
DR   InterPro; IPR011510; SAM_2.
DR   Pfam; PF00870; P53; 1.
DR   Pfam; PF07710; P53_tetramer; 1.
DR   Pfam; PF07647; SAM_2; 1.
DR   PRINTS; PR00386; P53SUPPRESSR.
DR   ProDom; PD002681; P53; 1.
DR   SMART; SM00454; SAM; 1.
DR   PROSITE; PS00348; P53; 1.
DR   PROSITE; PS50105; SAM_DOMAIN; FALSE_NEG.
KW   Activator; Alternative promoter usage; Alternative splicing;
KW   Apoptosis; Developmental protein; DNA-binding; Metal-binding;
KW   Notch signaling pathway; Nuclear protein; Phosphorylation;
KW   Transcription; Transcription regulation; Ubl conjugation; Zinc.
FT   CHAIN         1    680       Tumor protein p73-like.
FT                                /FTId=PRO_0000185731.
FT   DOMAIN      541    607       SAM.
FT   DNA_BIND    170    362       By similarity.
FT   REGION        1    107       Transcription activation (By similarity).
```

Exhibit A

```
FT   REGION      352     388       Interaction with HIPK2 (By similarity).
FT   REGION      394     443       Oligomerization (By similarity).
FT   REGION      610     680       Transactivation inhibition (By
FT                                 similarity).
FT   COMPBIAS    437     444       Poly-Gln.
FT   METAL       244     244       Zinc (By similarity).
FT   METAL       247     247       Zinc (By similarity).
FT   METAL       308     308       Zinc (By similarity).
FT   METAL       312     312       Zinc (By similarity).
FT   CROSSLNK    676     676       Glycyl lysine isopeptide (Lys-Gly)
FT                                 (interchain with G-Cter in SUMO) (By
FT                                 similarity).
FT   VARSPLIC      1     108       MNFETSRCATLQYCPDPYIQRFIETPSHFSWKESYYRSAMS
FT                                 QSTQTSEFLSPEVFQHIWDFLEQPICSVQPIDLNFVDEPSE
FT                                 NGATNKIEISMDCIRMQDSDLSDPMW -> MLYLESNAQTQ
FT                                 FSE (in isoform 2, isoform 4 and isoform
FT                                 6).
FT                                 /FTId=VSP_012475.
FT   VARSPLIC      1      21       MNFETSRCATLQYCPDPYIQR -> MPSC (in isoform
FT                                 7, isoform 8 and isoform 9).
FT                                 /FTId=VSP_012476.
FT   VARSPLIC    450     680       QTSMQSQSSYGNSSPPLNKMNSMNKLPSVSQLINPQQRNAL
FT                                 TPTTMPEGMGANIPMMGTHMPMAGDMNGLSPTQALPPPLSM
FT                                 PSTSHCTPPPPYPTDCSIVSFLARLGCSSCLDYFTTQGLTT
FT                                 IYQIEHYSMDDLASLKIPEQFRHAIWKGILDHRQLHDFSSP
FT                                 PHLLRTPSGASTVSVGSSETRGERVIDAVRFTLRQTISFPP
FT                                 RDEWNDFNFDMDSRRNKQQRIKEEGE -> HLLSACFRNEL
FT                                 VESRREAPTQSDVFFRHSNPPNHSVYP (in isoform
FT                                 5, isoform 6 and isoform 9).
FT                                 /FTId=VSP_012477.
FT   VARSPLIC    551     680       SFLARLGCSSCLDYFTTQGLTTIYQIEHYSMDDLASLKIPE
FT                                 QFRHAIWKGILDHRQLHDFSSPPHLLRTPSGASTVSVGSSE
FT                                 TRGERVIDAVRFTLRQTISFPPRDEWNDFNFDMDSRRNKQQ
FT                                 RIKEEGE -> RIWQV (in isoform 3, isoform 4
FT                                 and isoform 8).
FT                                 /FTId=VSP_012478.
SQ   SEQUENCE   680 AA;  76760 MW;  AC45DABB88F61400 CRC64;

  Query Match             96.4%;  Score 2991;  DB 1;  Length 680;
  Best Local Similarity   98.3%;  Pred. No. 1.3e-186;
  Matches  562;  Conservative    5;  Mismatches    5;  Indels    0;  Gaps    0;

Qy         15 PQYTNLGLLNSMDQQIQNGSSSTSPYNTDHAQNSVTAPSPYAQPSSTFDALSPSPAIPSN 74
              ||||||||| ||||||||||||||||||||||||||||||||||||||||||||||||||
Db        109 PQYTNLGLLNGMDQQIQNGSSSTSPYNTDHAQNSVTAPSPYAQPSSTFDALSPSPAIPSN 168

Qy         75 TDYPGPHSFDVSFQQSSTAKSATWTYSTELKKLYCQIAKTCPIQIKVMTPPPQGAVIRAM 134
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        169 TDYPGPHSFDVSFQQSSTAKSATWTYSTELKKLYCQIAKTCPIQIKVMTPPPQGAVIRAM 228

Qy        135 PVYKKAEHVTEVVKRCPNHELSREFNEGQIAPPSHLIRVEGNSHAQYVEDPITGRQSVLV 194
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        229 PVYKKAEHVTEVVKRCPNHELSREFNEGQIAPPSHLIRVEGNSHAQYVEDPITGRQSVLV 288

Qy        195 PYEPPQVGTEFTTVLYNFMCNSSCVGGMNRRPILIIVTLETRDGQVLGRRCFEARICACP 254
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        289 PYEPPQVGTEFTTVLYNFMCNSSCVGGMNRRPILIIVTLETRDGQVLGRRCFEARICACP 348

Qy        255 GRDRKADEDSIRKQQVSDSTKNGDGTKRPFRQNTHGIQMTSIKKRRSPDDELLYLPVRGR 314
              |||||||||||||||||| |||||||||||||||||||||||||||||||||||||||||
Db        349 GRDRKADEDSIRKQQVSDSAKNGDGTKRPFRQNTHGIQMTSIKKRRSPDDELLYLPVRGR 408

Qy        315 ETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSIQSPSSYGNSSPPLNK 374
              |||||||||||||||||||||||||||||||||||||||||:|| ||||||||||||
Db        409 ETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQHQHLLQKQTSMQSQSSYGNSSPPLNK 468
```

Exhibit A

```
Qy        375 MNSMNKLPSVSQLINPQQRNALTPTTIPDGMGANIPMMGTHMPMAGDMNGLSPTQALPPP 434
              ||||||||||||||||||||||||||:|:||||||||||||||||||||||||||||||||
Db        469 MNSMNKLPSVSQLINPQQRNALTPTTMPEGMGANIPMMGTHMPMAGDMNGLSPTQALPPP 528

Qy        435 LSMPSTSHCTPPPPYPTDCSIVSFLARLGCSSCLDYFTTQGLTTIYQIEHYSMDDLASLK 494
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        529 LSMPSTSHCTPPPPYPTDCSIVSFLARLGCSSCLDYFTTQGLTTIYQIEHYSMDDLASLK 588

Qy        495 IPEQFRHAIWKGILDHRQLHEFSSPSHLLRTPSSASTVSVGSSETRGERVIDAVRFTLRQ 554
              ||||||||||||||||||||:|||| ||||||| ||||||||||||||||||||||||||
Db        589 IPEQFRHAIWKGILDHRQLHDFSSPPHLLRTPSGASTVSVGSSETRGERVIDAVRFTLRQ 648

Qy        555 TISFPPRDEWNDFNFDMDARRNKQQRIKEEGE 586
              ||||||||||||||||||:||||||||||||
Db        649 TISFPPRDEWNDFNFDMDSRRNKQQRIKEEGE 680
```

<!--EndFragment-->